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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/629,719	08/01/2000	Teruna J. Siahaan	30406	5579

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EXAMINER
HADDAD, MAHER M

ART UNIT	PAPER NUMBER
1644	

DATE MAILED: 03/11/2003

19

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/629,719	SIAHAAN ET AL.	
	Examiner	Art Unit	
	Maher M. Haddad	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 February 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,4-9,35 and 37-42* is/are pending in the application.

4a) Of the above claim(s) *4,5 and 39-41* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,6-9, 35, 37, 38 and 42* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

RESPONSE TO APPLICANT'S AMENDMENT

1. Applicant's amendment, filed 2/4/03 (Paper No. 17), is acknowledged.

2. Claims 4-5 and 39-41 stand withdrawn from further consideration by the Examiner, 37 C.F.R. § 1.142(b) as being drawn to a nonelected invention.

3. Claims 1-2, 6-9, 35, 37-38 and 42 are under examination as they read on an a conjugate comprising a drug coupled with an isolated peptide sequence, wherein the peptide is SEQ ID NO:8 and the drug is methotrexate as the species.

4. The first paragraph of the brief description of the drawings section of the specification should be amended to insert the following paragraph:

> The patent or application file contains at least one drawing executed in color. Copies of this patent or patent application publication with color drawing(s) will be provided by the U.S. Patent and Trademark Office upon request and payment of the necessary fee.

5. The amendment filed 07/03/02 stand objected to under 35 U.S.C. 132 because it introduces new matter into the disclosure. 35 U.S.C. 132 states that no amendment shall introduce new matter into the disclosure of the invention. The added material which is not supported by the original disclosure is as follows:

The preliminary amendment filed on 07/03/02 to the Sequence Listing and computer readable Form substituting the original Sequence Listing represents a departure from the specification and the claims as originally filed. Applicant does not points out for support for the newly added limitation "Xaa is penicillamine". However, the specification and the claims as originally filed have no support for the new added matter "Xaa is penicillamine". It is noted in the specification, page 17, line 16 that SES ID NO:2 shows show N-terminal Pen, however, no support was found for other SEQ ID NOS: 1 and 3-8.

Applicant is required to cancel the new matter in the response to this Office action.

6. In view of the amendment filed on 2/04/03 (Paper No.17), only the following rejections are remained.

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> *The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.*

8. Claims 9 and 42 stand rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a conjugate comprising a methotrexate (MTX) and the

drugs recited in claim 7 coupled with a peptide of SEQ ID NO: 1-8 which derived from ICAM-1 and LFA-1; does not reasonably provide **enablement** for a conjugate wherein the peptide sequence **having** at least about 50% homology with SEQ ID NO:8 in claim 9, or any conjugate comprising a first portion and a second portion wherein said first portion is **any** peptide and said second portion is a drug, said peptide being derived from ICAM-1 or LFA-1 and being characterized by binding to LFA-1 or ICAM-1 receptors on leukocytes and by being internalized by cells expressing at least one of said receptors in claim 42. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims essentially for the same reasons set forth in the previous Office Action, paper No. 16, mailed 11/05/02.

Applicant's arguments, filed 2/04/03 (Paper No. 17), have been fully considered, but have not been found convincing.

Applicant argues that the amendment to the claims overcome the 35 U.S. C 112, first paragraph.

Applicant arguments are found compelling, however, Applicant did not address the 50% homology issue in claim 9 and the conjugate wherein first portion is **any** peptide derived from ICAM-1 or LFA- and being characterized by binding to LFA-1 or ICAM-1 receptors in claim 42 of the rejection.

9. Claims 9 and 42 stand rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention essentially for the same reasons set forth in the previous Office Action, paper No. 16, mailed 11/05/02.

Applicant's arguments, filed 2/04/03 (Paper No. 17), have been fully considered, but have not been found convincing.

Applicant argues that the amendment to the claims overcome the 35 U.S. C 112, first paragraph.

Applicant arguments are found compelling, however, Applicant did not address the 50% homology issue in claim 9 and the conjugate wherein first portion is **any** peptide derived from ICAM-1 or LFA- and being characterized by binding to LFA-1 or ICAM-1 receptors in claim 42 of the rejection.

10. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

11. Claims 1-2, 6-9, 35, 37-38 and 42 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Gursoy *et al* (April 1999) (IDS reference No.2) in view of Nagy *et al* (1993) essentially for the same reasons set forth in the previous Office Action, paper No. 16, mailed 11/05/02.

Applicant's arguments, filed 2/04/03 (Paper No. 17), have been fully considered, but have not been found convincing.

Applicant argues that Gursoy *et al* does not teach (1) peptides consisting of SEQ ID NO:1-8, (2) the peptides can be conjugated with drugs. Applicant further argues that Nagy et al, discloses that methotrexate can be covalently conjugated to sematostatin analog or two analogs of luteinizing hormone-releasing hormone. Furhter, Nagy *et al* does not disclose (1) peptides consisting of SEQ ID NO:1-8, (2) the peptides can be conjugated with drugs. Applicant concluded that the references when combined do not teach or suggest that peptides consisting of SEQ ID NO: 1-8 could be conjugated to drugs. In addition, Applicant argues that the motivation to combine provides generalized scientific goals that cannot substitute for the particularity needed to establish a prima facie case of obviousness. Furthermore, Applicant argues that in the absence of some teaching or suggestion in the cited references concerning the [method] conjugate of the present invention, the examiner has presented no more than an improper hindsight reconstruction of the present invention. Finally, Applicant argues that the cited references do not provide a motivation to combine the references as suggested by the Examiner.

Contrary to Applicant assertions, Gursoy *et al* teach a conjugate comprising a 12 amino acid cyclic peptide consisting of SEQ ID NO: 8, that is Cyclo (1, 12)-Pen1-Pro2-Arg3-Gly4-Gly5-Ser6-Val7-Leu8-Val9-Thr10-Gly11-Cys12-OH (cIBR) having 100% homology to SEQ ID NO: 8 and derived from ICAM-1, and a fluorescence-labeled peptide (FITC-cIBR). The conjugate characterized by the ability of binding to surface receptor of target leukocyte Molt-3 T cells and subsequently being internalized by said target cells. Gursoy et al further teach that the peptide of the conjugate include at least one non-natural amino acid penicillamin at amino acid position 1 (see entire document and page 414 under abstract and page 415 right column 2nd paragraph in particular). Finally Gursoy et al teach that the drug conjugated to a ligand molecule that can bind to receptors on the surface of the target cells so that the drug directed specifically to the target cells that express the receptors. The binding and internalization of cIBR peptide can be utilized as a method of targeted drug delivery to leukocytes for the treatment of leukocyte-related diseases (see abstract and page 414 left column 2nd paragraph in particular).

Furthermore, Nagy *et al* teach that methotrexate is an antineoplastic agent and chemically suitable for conjugation to peptides (see page 6373, right column 2nd paragraph in particular). Further, Nagy *et al* teach that such conjugates can be used as carrier molecules for different chemotherapeutic agents in cases in which direct action of these peptides on the membrane receptors could be established. (page 6376, right column, paragraph 1 in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to conjugate the peptide taught by the Gursoy *et al* with the drug methotrexate taught by Nagy *et al.* It is prima facie obvious to combine two compositions each of which is taught by prior art to be useful for same purpose in order to form third composition that is to be used for very same purpose; idea of combining them flows logically from their having been individually taught in prior art. In re Kerkhoven, 205 USPQ 1069, CCPA 1980. See MPEP 2144.06.

Further, specific statements in the references themselves which would spell out the claimed invention are not necessary to show obviousness, since questions of obviousness involves not only what references expressly teach, but what they would collectively suggest to one of ordinary skill in the art. See CTS Corp. v. Electro Materials Corp. of America 202 USPQ 22 (DC SNY); and In re Burckel 201 USPQ 67 (CCPA).

In addition, the motivation to combine can arise from the expectation that the prior art elements will perform their expected functions to achieve their expected results when combine for their common known purpose. Section MPEP 2144.07.

In response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. In re McLaughlin , 443 F.2d 1392, 170 USPQ 209 (CCPA 1971). See MPEP 2145.

12. No claim allowed

13. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

14. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maher Haddad, whose telephone number is (703) 306-3472. The examiner can normally be reached Monday to Friday from 8:00 to 4:30. A message may be left on the

examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached at (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.

Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-3014.

Maher Haddad, Ph.D.
Patent Examiner
Technology Center 1600
March 10, 2003

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